FORM PTO-1390 (REV 10-95) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES PATENT AND TRADEMARK OFFICE DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
PC9455A

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)
Not yet assigned 09/508892

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP98/05720	April 9, 1998 (04.09.1998)	From GB No. 9720228.7 filed September 23, 1997 (09/23/1997) and From GB No. 9810143.9 filed May 12, 1998 (05/12/1998)

TITLE OF INVENTION
PARASITICIDAL FORMULATIONS

APPLICANT(S) FOR DO/EO/US
Hiep HUATAN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is the **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☒ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. To 16. Below concern other documents(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
    ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

EXPRESS MAIL NO. EL628218485

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Not yet assigned 09/508892	PCT/EP98/05720	PC9455A

17. ☒ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5)):		
☒ Search Report has been prepared by the EPO or JPO $840.00		
☐ International preliminary examination fee paid to USPTO (37CFR 1.482).. .....$670.00		
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1 445(a)(2)).....$760.00		
☐ Neither international preliminary examination fee (37 CFR 1 482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $970.00		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....$ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	21 - 20 =	1	X $ 18.00	$18.00	
Independent Claims	4 - 3 =	1	X $ 78.00	$78.00	
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ $260.00	$260.00	
TOTAL OF ABOVE CALCULATIONS =				$356.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note: 37 CFR 1.9, 1.27, 1.28)				$	
SUBTOTAL =				$1,196.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$40.00	
TOTAL FEES ENCLOSED =				$1,236.00	
				Amount to be: Refunded	$
				Charged	$

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 16-1445 in the amount of $ 1,236.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.16-1445. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Lorraine B Ling
Signature

Lorraine B. Ling
Name

35,251
Registration Number

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Hiep Huatan :

APPLICATION NO.: Not Yet Assigned :

FILING DATE: Herewith :

TITLE: PARASITICIDAL FORMULATIONS :

Examiner: Not Yet Assigned

Group Art Unit: Not Yet Assigned

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend as follows:

In the Specification:

In the specification, on page 1, line 1 insert:

--- Cross Reference to Related Applications

This application is the National Stage of International Application No. PCT/EP98/05720, filed April 9, 1998.

Field of the Invention ---

In the specification, on page 1, line 6 insert:

--- Background of the Invention ---

In the specification, on page 2, line 22 insert:

--- Summary of the Invention ---

In the specification, on page 5, line 15 insert:

--- Brief Description of the Drawings ---

Figure 1 shows the blood plasma levels in cattle achieved by the implants prepared in Examples 1 and 2.

Figure 2 shows the degradation profiles of implants prepared in Example 4.

Detailed Description of the Invention ---.

EXPRESS MAIL NO. EL628218485US

In the Claims:

Claim 3. (Amended) An implant as claimed in claim 1 [or claim 2,] wherein the parasiticidal compound has an aqueous solubility below 100 µg/ml.

Claim 4. (Amended) An implant as claimed in [claim 3,] claim 1, wherein the parasiticidal compound is an avermectin or a milbemycin.

Claim 5. (Amended) An implant as claimed in [claim 4,] claim 1, wherein the parasiticidal compound is doramectin.

Claim 6. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 wherein the bulking agent is lactose.

Claim 7. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 wherein the tabletting excipients include magnesium stearate.

Claim 8. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 wherein the tabletting excipients include a tablet disintegrant.

Claim 9. (Amended) An implant as claimed in claim 8, wherein the tablet disintegrant is sodium starch glycolate.

Claim 10. (Amended) An implant as claimed [any one of the preceding claims,] claim 1 which contains an antioxidant or a reducing agent.

Claim 11. (Amended) An implant as claimed in [claim 10,] claim 1, wherein the antioxidant is butylated hydroxy toluene or butylated hydroxy anisole.

Claim 12. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 which is suitable for sterilization, or has been sterilized, by irradiation.

Claim 13. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 wherein the tabletting excipients include polyvinyl pyrrolidone.

Claim 14. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 wherein the parasiticidal compound makes up between 10 and 60% of the implant, by weight.

Claim 15. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 which is adapted for implantation into the ears of cattle or sheep.

Claim 16. (Amended) An implant as claimed in [any one of the preceding claims,] claim 1 which is rod-shaped.

Claim 17. (Amended) [Use] A process comprising the use of an antioxidant or a reducing agent in a formulation containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin.

Claim 18. (Amended) The [use] process as claimed in claim 17, wherein the formulation is suitable for sterilization, or has been sterilized, by irradiation.

Claim 19. (Amended) The [use] process as claimed in claim 17 or claim 18, wherein the formulation is not liquid.

Claim 21. (Amended) A method for the treatment or prevention of parasitic infections which comprises administering an implant as defined in [any one of claims 1-16] claim 1 to an animal in need of such treatment.

R E M A R K S

This preliminary amendment is being submitted to conform the present application which is the National Stage of International Application No. PCT/EP98/05720 to U.S. recommended format. No new subject matter has been added.

Applicant believes the present application contains patentable subject matter and earnestly requests allowance of all of the claims.

Respectfully,

Date: March 17, 2005

Lorraine B. Ling
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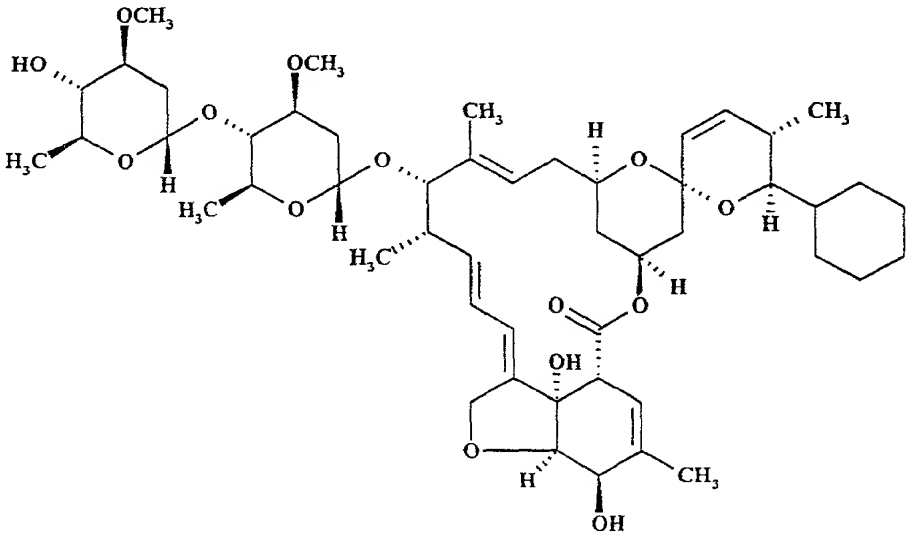
Parasiticidal formulations

This invention relates to a solid implant containing a parasiticidal compound having low aqueous solubility, which is particularly useful for administration to livestock such as cattle, pigs and sheep.

A number of potent macrocyclic parasiticidal compounds are known, including the avermectins and milbemycins. UK Patent N° 1,573,955 discloses a family of avermectin compounds (including avermectins B1a and B1b) which are indicated as parasiticides.

22,23-Dihydroavermectin B1 (ivermectin, disclosed in EP 1689) is available commercially in an injectable formulation (sold as IVOMEC™). Ivermectin is a mixture of at least 80% 22,23-dihydroavermectin B1a (having a 25-sec butyl group) and not more than 20% of 22,23-dihydroavermectin B1b (having a 25-isopropyl group).

25-Cyclohexyl-avermectin B1 (doramectin, disclosed in EP 214731) has the following structure,



and is available commercially in an oil formulation for injection (sold as DECTOMAX™) for the treatment and prevention of internal and external parasite infestations in cattle. The oil formulation is described in European Patent N° 393890.

The milbemycins are similar in structure to the avermectins, except that they are unsubstituted at the 13-position.

Although formulations such as DECTOMAX™ have been successful, there is a need for further formulations which are convenient to administer and which provide prolonged protection against parasites.

European Patent Application 240274 discloses the use of avermectins as growth promoting agents. European Patent Application 311195 discloses the use of avermectins in the prevention of fescue toxicosis in grazing animals. In both documents, a subcutaneous implant is claimed, but no teaching is provided about how such an implant would be produced.

European Patent Application 473223 discloses a complex bioerodible implant in which active agents such as anthelmintics are incorporated covalently into a chain backbone of a constituent polymer.

European Patent Application 537998 discloses a drug delivery device compounded of a polymeric matrix, a vehicle (which is a plasticizing solvent for the polymeric matrix) and a drug. The drug may be an avermectin or a milbemycin, and the device is intended for topical delivery of drugs, such as a flea or tick collar for pets.

Thus, according to the present invention, there is provided a solid implant comprising at least one parasiticidal compound having low aqueous solubility; and tabletting excipients including a bulking agent.

An important feature of the implants of the present invention is their simplicity. Preferably therefore, greater than 95% by weight of the implant is made up of parasiticidal compound and tabletting excipients, more preferably greater than 99% by weight.

Implants according to the invention may be implanted intramuscularly. Preferably however, they are implanted subcutaneously (i.e. into the fatty tissue directly below the skin).

Suitable parasiticidal compounds are those having an aqueous solubility below 100 μg/ml, for example the avermectins and milbemycins. Doramectin is of particular interest (which has an aqueous solubility of 0.6 μg/ml at pH 7). Ivermectin is also of interest.

Preferably, the bulking agent is lactose. Other suitable bulking agents include other sugars, microcrystalline cellulose (which is available commercially as AVICEL™) and dicalcium phosphate.

Other tabletting excipients which may be present include magnesium stearate, which acts as a lubricant to facilitate tabletting. Typically, magnesium stearate will make up about 3% of the implant, by weight. Binding agents may also be included in the formulation to aid granulation and compressibility. Examples of binding agents include starch, gelatin and polyvinyl pyrrolidone. Typically, the binding agent, when present, will make up between 2 to 10% of the implant, by weight.

A further tabletting excipient which the implants of the invention may optionally contain is a tablet disintegrant. Suitable tablet disintegrants include sodium starch glycolate, which is available commercially as EXPLOTAB™. Other disintegrants which may be mentioned are dicalcium phosphate and cross-linked starch. Typically, the disintegrant, when present, will make up about 5% of the implant, by weight.

Preferably, the parasiticidal compound (or compounds) makes up between 10 and 60% of the implant, by weight, more preferably from 20 to 45% of the implant, by weight, for example 40%.

Preferably, the implants of the invention contain an antioxidant or a reducing agent. It has been found that such additives reduce or eliminate degradation of the parasiticidal compound, thus extending the shelf-life of the implant. It has been found that such

additives are particularly useful for stabilizing the parasiticidal compound when the implant is sterilized by irradiation, such as gamma or beta irradiation.

Antioxidants of particular interest are butylated hydroxy anisole (BHA; a mixture of 2-*tert*-butyl-4-methoxyphenol and 3-*tert*-butyl-4-methoxyphenol) and butylated hydroxy toluene (BHT; 2,6-di-*tert*-butyl-4-methylphenol). Other antioxidants and reducing agents include alpha-tocopherol, alkyl gallate derivatives, nordihydroguaiaretic acid, ascorbic acid, sodium metabisulphate and sodium sulphite. Typically, the antioxidant, when present, will make up between 0.01 to 0.5% of the implant, by weight, more preferably 0.1 to 0.2%.

As mentioned above, the implants of the invention may be irradiated to sterilize them, typically at a dose in the range 15-25 kGy (kilo Gray).

The implants of the invention may be implanted in various parts of the animal to be treated, for example the flank, the base of the tail or the ear. Where the ears are removed during a meat rendering process, this is a preferred site for implantation.

To facilitate such implantation, the implants are preferably rod-shaped, and can be implanted conveniently using a conventional hand-operated implant gun. Suitably, rod-shaped implants are 2 to 30 mm in length, and 2 to 5 mm in diameter. Preferred dimensions are 5 to 6 mm in length, and 2 to 3 mm in diameter. Preferably, the cross section is circular.

According to the invention, there is also provided a method for the treatment or prevention of parasitic infections which comprises administering an implant as defined above to an animal in need of such treatment.

Parasitic infections of particular interest are those caused by endoparasites including helminthiasis (most frequently caused by nematode worms in the gastrointestinal tract). The implants are also useful in treatment or prevention of ectoparasite infections such as of ticks, mites, lice, fleas, blowfly, biting insects and migrating dipterous larvae.

The dosage to be administered will depend on the animal to be treated, the parasiticidal compound being used, and the condition to be treated. However, a suitable dose of doramectin is 0.5 mg/kg of animal body weight. Typically, an implant according to the invention having the preferred dimensions mentioned above will contain about 10 mg of doramectin. Thus, for cattle weighing 120 kg, 6 implants will be needed. This could provide sustained release of doramectin for up to 120 days. Where multiple implants are required, these can often be implanted consecutively by a single actuation of an implant gun.

Because implants according to the present invention can provide sustained release in cattle over an entire grazing season, administration need only take place once a year. Therefore, the invention provides the use of an avermectin or a milbemycin compound in the manufacture of an implant for treatment or prevention of parasitic infections, characterized in that the medicament is administered once a year.

The implants of the invention may be prepared by dry- or wet-mass granulation followed by milling and compression into the desired shape using conventional techniques.

For example, an implant consisting of doramectin, lactose and magnesium stearate could be prepared by dry-mass granulation using the following steps:

1. Blend components except magnesium stearate
2. Sieve through a screen
3. Blend
4. Add half of magnesium stearate
5. Blend
6. Compress into slugs
7. Mill slugs to granules
8. Collect desired size fraction of granules
9. Blend
10. Add remaining magnesium stearate
11. Blend

12. Compress into rods

The steps for wet-mass granulation are similar, except that some components are sprayed onto other components while they are blending, in a solvent which is later removed. In addition, a binder is used to aid the adherence of the individual particles. For example, in the preparation of an implant containing BHA and the binder PVP, BHA and PVP can be added to a blending mixture of components by spraying as a solution in ethanol. Thus, an implant consisting of doramectin, lactose, sodium starch glycolate, BHA, PVP and magnesium stearate could be prepared by wet-mass granulation using the following steps:

1. Blend components except magnesium stearate, BHA and PVP
2. Sieve through a screen
3. Blend
4. Spray solution of BHA and PVP in ethanol onto mixture while mixing
5. Sieve wet mass
6. Dry to granules
7. Mill
8. Collect desired size fraction
9. Blend
10. Add magnesium stearate
11. Blend
12. Compress into rods

Thus, according to a further aspect of the invention, there is provided a process for the production of an implant as defined above, which comprises mixing the parasiticidal compound with the tabletting excipients and forming into the desired shape.

The duration of action of the implants of the invention may be determined by measuring blood plasma levels in cattle following implantation. These levels have been correlated with antiparasitic activity of the compounds which have established that for effective control of helminths a blood plasma level of about 2 ng/ml needs to be maintained, and that

for effective control of single-host ticks a blood plasma level of about 5 ng/ml needs to be maintained.

In a broader aspect, the invention further provides use of an antioxidant or a reducing agent in a composition containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin. Although BHA has been used previously in association with doramectin in DECTOMAX™, its function was to prevent rancidity of the oil formulation rather than to aid the stability of doramectin in solution. This aspect of the invention is particularly useful when the formulation is irradiated, and may be used in liquid and non-liquid formulations (such as solids and powders).

The invention is illustrated by the following examples, and the accompanying figures in which:

Figure 1 shows the blood plasma levels in cattle achieved by the implants prepared in Examples 1 and 2; and

Figure 2 shows the degradation profiles of implants prepared in Example 4.

Example 1

Doramectin implant

Components	Specification	mg/unit	% by weight
Doramectin[a]	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	14.250	57
Magnesium stearate	Ph Eur	0.750	3
Total		**25.000**	**100**

[a] mean particle size 19.27 μm (volume mean diameter)

The components, except magnesium stearate, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a further 15 minutes. After that, half of the magnesium stearate was added and blending

continued for 5 minutes, after which the blend was compressed to form "slugs". The slugs were then milled to form granules, and the size fraction 250-355 μm was collected.

The collected granules were then blended for 15 minutes, and then the remaining half of the magnesium stearate was added and blending continued for 5 minutes. The blend was then compressed on a suitable tablet machine using 2 mm tooling to produce rod-shaped implants of 2 mm diameter and 5 mm length.

Example 2

Doramectin implant containing a tablet disintegrant

Components	Specification	mg/unit	% by weight
Doramectin[a]	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	13.000	52
Sodium starch glycolate (EXPLOTAB™)	BP	1.250	5
Magnesium stearate	Ph Eur	0.750	3
Total		**25.000**	**100**

[a] mean particle size 19.27 μm (volume mean diameter)

The implants were prepared by the method of Example 1.

Example 3

Pharmacokinetic profiling

The implants of Examples 1 and 2 were implanted into 16 cows at a dose of 500μg/kg. The blood plasma concentrations of doramectin following implantation were measured, and the results are shown in Figure 1. It can be seen that in each case single-host tick activity was obtained for more than 50 days, and control of helminths was obtained for about 90 days.

Example 4

Doramectin implant containing an antioxidant

Components	Specification	mg/unit	% by weight
Doramectin[a]	Pfizer	10.000	40
β-anhydrous lactose	Ph Eur	11.625	46.5
Sodium starch glycolate (EXPLOTAB™)	BP	1.250	5
Butylated hydroxy anisole	Ph Eur	0.125	0.5
Polyvinyl pyrrolidone	Ph Eur	1.250	5
Magnesium stearate	Ph Eur	0.750	3
Total		**25.000**	**100**

The components, except magnesium stearate, butylated hydroxy anisole and polyvinyl pyrrolidone, were blended together in a blender for 15 minutes. The blend was then sieved through a 680 μm mesh screen and blended for a further 15 minutes. After that, the butylated hydroxy anisole and polyvinyl pyrrolidone was dissolved in ethanol to form the granulation fluid. The volume of ethanol used was approximately 20%, by volume, of the total formulation. The granulation fluid was sprayed onto the blend under constant mixing over 10 minutes. The resultant wet granule mass was sieved through a 1.4 mm mesh screen and allowed to dry under vacuum for 3 hours at 50°C. The dried granules were then milled, and the size fraction 250-355 μm was collected.

The collected granules were then blended for 15 minutes, and the magnesium stearate was added and blending continued for a further 5 minutes. The blend was then compressed on a suitable tabletting machine using a 2mm tooling to produce rod-shaped implants of 2mm diameter and 5 mm length.

These implants were used in stability studies, in which the effects of BHA and electron beam irradiation were investigated. Implants containing 0.5% w/w BHA and having been treated at four different irradiation levels [control (0 kGy), 15 kGy, 20 kGy and 25 kGy]

were stored at 30°C for 30 weeks, and then the percentage of doramectin remaining was determined. A control implant containing no BHA was also studied.

The results are shown in Figure 2. It can be seen that the presence of BHA dramatically improves the stability of the implants on storage, even when the implants have been irradiated.

Claims:

1. A solid implant comprising at least one parasiticidal compound having low aqueous solubility; and tabletting excipients including a bulking agent.

2. An implant as claimed in claim 1, which is adapted for subcutaneous implantation.

3. An implant as claimed in claim 1 or claim 2, wherein the parasiticidal compound has an aqueous solubility below 100 μg/ml.

4. An implant as claimed in claim 3, wherein the parasiticidal compound is an avermectin or a milbemycin.

5. An implant as claimed in claim 4, wherein the parasiticidal compound is doramectin.

6. An implant as claimed in any one of the preceding claims, wherein the bulking agent is lactose.

7. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include magnesium stearate.

8. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include a tablet disintegrant.

9. An implant as claimed in claim 8, wherein the tablet disintegrant is sodium starch glycolate.

10. An implant as claimed in any one of the preceding claims, which contains an antioxidant or a reducing agent.

11. An implant as claimed in claim 10, wherein the antioxidant is butylated hydroxy toluene or butylated hydroxy anisole.

12. An implant as claimed in any one of the preceding claims, which is suitable for sterilization, or has been sterilized, by irradiation.

13. An implant as claimed in any one of the preceding claims, wherein the tabletting excipients include polyvinyl pyrrolidone.

14. An implant as claimed in any one of the preceding claims, wherein the parasiticidal compound makes up between 10 and 60% of the implant, by weight.

15. An implant as claimed in any one of the preceding claims, which is adapted for implantation into the ears of cattle or sheep.

16. An implant as claimed in any one of the preceding claims, which is rod-shaped.

17. Use of an antioxidant or a reducing agent in a formulation containing an avermectin or a milbemycin for preventing degradation of the avermectin or milbemycin.

18. The use as claimed in claim 17, wherein the formulation is suitable for sterilization, or has been sterilized, by irradiation.

19. The use as claimed in claim 17 or claim 18, wherein the formulation is not liquid.

20. A process for the production of an implant as defined in claim 1, which comprises mixing the parasiticidal compound with the tabletting excipients and forming into the desired shape.

21. A method for the treatment or prevention of parasitic infections which comprises administering an implant as defined in any one of claims 1-16 to an animal in need of such treatment.

22. An implant as claimed in claim 1, wherein greater than 95% by weight of the implant is made up of parasiticidal compound and tabletting excipients.

23. An implant as claimed in claim 22, wherein greater than 99% by weight of the implant is made up of parasiticidal compound and tabletting excipients.

24. A process for the production of an implant as defined in claim 12, which comprises mixing the parasiticidal compound with the tabletting excipients and an antioxidant or a reducing agent; forming into the desired shape; and sterilizing by irradiation.

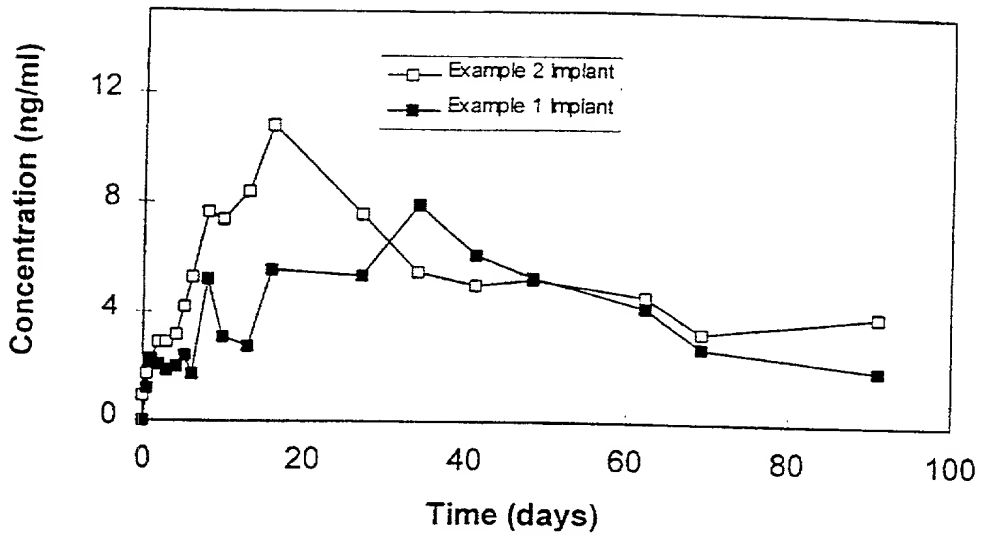

Example 2 Implant
Example 1 Implant
Concentration (ng/ml)
12
8
4
0
0
20
40
60
80
100
Time (days)

Figure 1

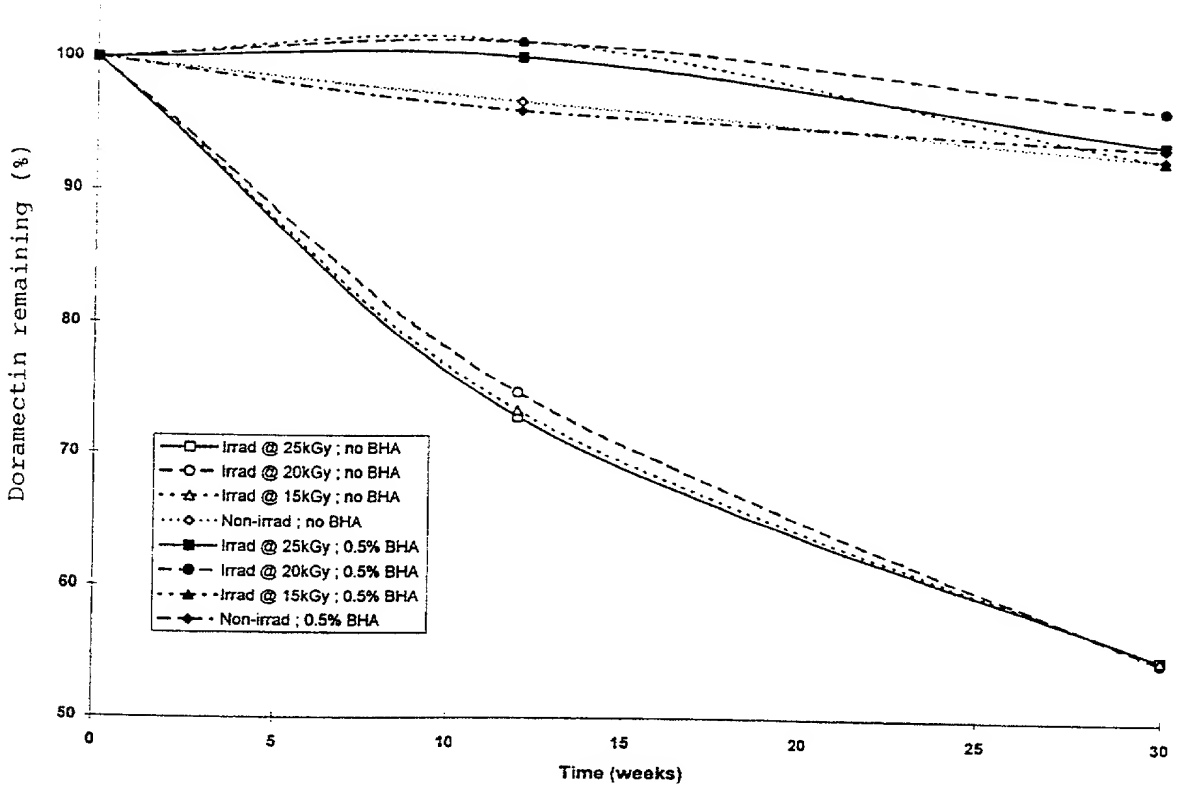

Doramectin remaining (%)
100
90
80
70
60
50
0
5
10
15
20
25
30
Time (weeks)
Irrad @ 25kGy ; no BHA
Irrad @ 20kGy ; no BHA
Irrad @ 15kGy ; no BHA
Non-irrad ; no BHA
Irrad @ 25kGy ; 0.5% BHA
Irrad @ 20kGy ; 0.5% BHA
Irrad @ 15kGy ; 0.5% BHA
Non-irrad ; 0.5% BHA

Figure 2

PTO/SB/01(12/97)
Approved for use through 09/30/2000 OMB 0651-0032
Patent and Trademark Office U S DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box → [+]

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration submitted with Initial Filing

☐ Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (e)) required)

Attorney Docket Number	PC9455A
First Named Inventor	Hiep HUATAN
COMPLETE IF KNOWN	
Application Number	Not yet assigned
Filing Date	Filed herewith
Group Art Unit	Not yet assigned
Examiner Name	Not yet assigned

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PARASITICIDAL FORMULATIONS

(Title of the Invention)

the specification of which
☐ is attached hereto
OR
☒ was filed on (MM/DD/YYYY) 09/04/1998 as United States Application Number or PCT International

Application Number PCT/EP98/05720 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
9720228.7	GB	09/23/1997	☐	☒	☐
9810143.9	GB	05/12/1998	☐	☒	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below:

Application Number(s)	Filing Date (MM/DD/YYYY)	
		☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B sheet attached hereto.

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DECLARATION ---- Utility or Design Patent Application

I hereby claim the benefit under 35 U S C 120 of any United States application(s), or 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 U S C 1 56, which became available between the filing date of the prior application and the national or PCT International filing date of this application.

U.S. Parent Application Number or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)
PCT/EP98/05720	09/04/1998	

☐ Additional U.S or PCT International application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith ☐ Customer Number or ☒ Registered practioner(s) name/registation number listed below 34

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☐ Additional registered practitioner(s) named on supplemental Registered Practitioner Information sheet PTO/SB/02C attached hereto

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U S C 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Hiep	HUATAN

Inventor's Signature	Hiep Huatan					Date	10/3/00
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☒ Additional inventors are being named on the ____ a supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto.